UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte LEX M. COWSERT, BRENDA F. BAKER, JOHN MCNEIL, SUSAN M. FREIER, HENRI M. SASMOR, DOUGLAS G. BROOKS, CARA OHASHI, JACQUELINE R. WYATT, ALEXANDER H. BORCHERS, and TIMOTHY A. VICKERS

Appeal 2007-1146
Application 09/295,463
Technology Center 1600

Decided: June 11, 2007

Before ERIC GRIMES, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to computer-modeling and robotically testing compounds, such as oligonucleotides. The Examiner has rejected the claims as having new matter and being obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse the new matter rejection but affirm the obviousness rejection.

BACKGROUND

"Oligonucleotide compounds are commonly used *in vitro* as research reagents and diagnostic aids, and *in vivo* as therapeutic and bioactive agents" (Specification 2). Oligonucleotides "complementary to the 'sense' strand of nucleic acids that encode polypeptides, are referred to as 'antisense oligonucleotides'" (*id.*).

"Traditionally, new chemical entities with useful properties are generated by (1) identifying a chemical compound (called a 'lead compound') with some desirable property or activity, (2) creating variants of the lead compound, and (3) evaluating the property and activity of such variant compounds" (*id.* at 2-3). However, this "traditional approach to generating active antisense compounds is limited by the relatively high cost and long time required to synthesize and screen a relatively small number of candidate antisense compounds" (*id.* at 3).

The Specification discloses "methods for automatically generating and screening active antisense compounds via robotic and other automated means" (*id.*). Initially, "all possible oligonucleotide sequences of [a] desired length capable of hybridizing to [a] target sequence . . . are generated" *in silico* (*id.* at 16). Then, "a series of thermodynamic, sequence, and homology scores are preferably calculated for each virtual oligonucleotide" (*id.*).

Using criteria that include the predicted ability to bind to functional regions within the target nucleic acid, sequences predicted to have therapeutic activity may be selected from the original population of virtual oligonucleotides (*id.* at 20-21). The selected virtual oligonucleotides are

then "synthesized on an automated synthesizer" (*id.* at 32) and their activities are assayed by methods "known in the art. For example, target RNA levels can be quantitated by, e.g., Northern blot analysis, competitive PCR, or reverse transcriptase polymerase chain reaction (RT-PCR)" (*id.* at 46).

DISCUSSION

1. CLAIMS

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are pending and on appeal. The claims have not been argued separately and therefore stand or fall together with respect to each ground of rejection. 37 C.F.R. § 41.37(c)(1)(vii).

We will focus on claims 55 and 59, which read as follows:

55. A method comprising:

a) generating *in silico* virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein synthetic compounds corresponding to said virtual compounds modulate the expression of said target nucleic acid sequence;

b) synthesizing compounds corresponding to at least some of said virtual compounds; and

c) robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59. A method comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria comprise a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target

> nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and
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> robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

Thus, claim 55 is directed to a method in which virtual compounds corresponding to actual compounds capable of modulating a target nucleic acid are generated. The virtual compounds are generated on the basis of their thermodynamic properties, and on either or both of (a) their ability to bind to functional regions of the target nucleic acid, and (b) whether they represent a uniform distribution of sequences when compared to the target nucleic acid. After the virtual compounds are generated, actual compounds corresponding to at least some of the virtual compounds are synthesized, and robotically assayed using either polymerase chain reaction (PCR), or enzyme-linked immunosorbent assay (ELISA).

"Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one." *Interactive Gift Express, Inc. v. Compuserve Inc.*, 231 F.3d 859, 875, 56 USPQ2d 1647, 1661 (Fed. Cir. 2000). Here, however, we conclude that the steps recited in claim 55 must be performed in the order recited, since steps (b) and (c) refer to "said virtual compounds" and "said synthetic compounds"; i.e., the virtual compounds generated in step (a) and the compounds synthesized in step (b).

Claim 59 is directed to a process in which virtual compounds are evaluated on the basis of the same properties recited in claim 55. After evaluation, synthetic compounds corresponding to at least some of the

virtual compounds are assayed for desired, physical, chemical, or biological properties.

2. PRIOR ART

The Examiner relies on the following references:

Agrafiotis	US 5,463,564	Oct. 31, 1995
Dower	US 5,639,603	Jun. 17, 1997
Harris	US 5,650,122	Jul. 22, 1997
Haff	US 5,720,923	Feb. 24, 1998

Eugen Uhlmann et al., *Antisense Oligonucleotides: A New Therapeutic Principle*, 90 Chemical Reviews 543-584 (June 1990).

3. NEW MATTER

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 stand rejected under 35 U.S.C. § 112, first paragraph, as containing new matter (Answer 3-5).[1]

The Examiner states that the amendment of August 4, 2003 introduced new matter into the claims (*id.* at 3). Specifically, the Examiner argues that the "limitation wherein said generating is practiced via the combination of a thermodynamic property 'and' the listed properties to control the generating step in claim 55" is new matter (*id.*). The Examiner argues that Figures 4-6 do not demonstrate possession of the claimed subject matter because they describe a process in which oligonucleotide sequences are generated before thermodynamic scores are determined (*id.* at 3-4).

Moreover, the Examiner argues, the figures depict performing the thermodynamic and targeting evaluations separately, "with no overlapping

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[1] Examiner's Answer, October 12, 2006.

or connecting elements which would lead one skilled in the art to interpret them as being performed in combination, as embodied by the limitations of the pending claims" (*id.* at 4). The Examiner argues that pages 19-24 similarly fail to support the claims because all evaluation is performed after the virtual compounds are generated "and is not performed as part of the generation step itself" (*id.*).

Appellants argue that the Specification, at page 7, lines 5-17, provides a general description of the invention that "quite clearly teach[es] provision or selection of a target nucleic acid sequence, followed by generation of a library of virtual compounds *in silico* according to defined criteria" (Br. 21, emphasis removed). Appellants argue that Figures 4-6 and pages 16-22 of the Specification present the criteria used to select the library of virtual compounds from the larger set of oligonucleotides initially generated (*id.*). Appellants argue that using these criteria to select desired sequences from the larger initial set of oligonucleotides can properly be considered "generation of 'in silico virtual compounds' as recited in claim 55, for example" (*id.* at 22, emphasis removed).

To satisfy the written description requirement, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). However, "claimed subject matter need not be described in haec verba in the specification in order for that specification to satisfy the description requirement." *In re Wright*, 866 F.2d 422, 425,

9 USPQ2d 1649, 1651 (Fed. Cir. 1989) (claim limitation lacking word-for-word support in the specification was not new matter because one skilled in the art would have recognized the limitation's presence in embodiments disclosed in the specification).

We agree with the Examiner that the Specification discloses that the invention has an initial step of generating "all possible oligonucleotide sequences of [a] desired length capable of hybridizing to [a] target sequence" *in silico* (Specification 16). We also agree that a subset is selected from the larger initial set of virtual compounds, by evaluating the virtual compounds' thermodynamic properties (*id.* at 16-19), ability to target functional regions of the target nucleic acid (*id.* at 20-21), and uniformity of distribution along the target sequence (*id.* 21-22).

Thus, the Specification describes a process in which a set of virtual compounds is selected using the criteria recited in claim 55. Although the Specification does not appear to use the term "generate," as does claim 55, to describe the process of selecting the compounds to be synthesized and tested, the Specification reasonably demonstrates that Appellants were in possession of a process having a step of "generating *in silico* virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof" as recited in claim 55.

We do not agree with the Examiner that by using the phrase "combinations thereof," claim 55 requires the thermodynamic and targeting evaluations to be performed simultaneously. Processes may be performed

sequentially, as disclosed in the Specification, and still be considered a combination.

We therefore reverse the Examiner's rejection of claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 as containing new matter.

4. OBVIOUSNESS

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 stand rejected under 35 U.S.C. § 103 as being obvious in view of Agrafiotis, Uhlmann, Dower, Haff, and Harris (Answer 5-7).

The Examiner cites Agrafiotis as "generically describ[ing] computerized design of a directed diversity chemical library, as well as computer-directed synthesis and testing of designed compounds for desired properties" (*id.* at 5). The Examiner points out that Agrafiotis "specifically teaches that his design, synthesis, and testing are iterative steps, and teaches testing and evaluation for desired chemical, biological and/or physical properties" (*id.* at 5-6). The Examiner notes that Agrafiotis discloses that the "chemical library thus designed may comprise a variety of different compounds, including drugs and bioactive compounds . . . , and . . . that it is well-known in the art for such libraries to comprise oligonucleotides as bioactive compounds" (*id.* at 6). The Examiner concedes that Agrafiotis "does not specifically teach design/evaluation according to the properties recited in the instant claims" (*id.*).

To meet this deficiency, the Examiner cites Uhlmann as "describ[ing] design of antisense molecules according to thermodynamic and 'other criteria' in order to achieve desired properties" (*id.*). The Examiner points out that Uhlmann "teach[es] synthesizing and testing for desired properties,

specifically hybridization/melting temperature (i.e. a thermodynamic property) and ability to bind to a target . . . [and] other desired properties, including stability and bioavailability" (*id.*).

The Examiner concedes that Uhlmann does not teach computer-controlled PCR or ELISA, and cites Haff and Harris, respectively, to demonstrate prior art knowledge of those processes (*id.*). The Examiner cites Dower as "teach[ing] automated synthesis and testing of oligonucleotides with desired properties, specifically those with desired hybridization and receptor binding properties (*id.*).

From these disclosures, the Examiner concludes that one of ordinary skill in the art would have considered it obvious to "have used the method of automated design and synthesis of drugs, as taught by AGRAFIOTIS, to design and synthesize the antisense drugs according to the thermodynamic and binding parameters taught by UHLMANN, combined with the synthesis steps taught by DOWER," in order "to facilitate design and testing of new drugs by rational drug design, as taught by UHLMANN" (*id.* at 7). The Examiner also concludes that it would have been obvious to assay the virtual antisense drugs so designed "using either the automated PCR or ELISA of HAFF or HARRIS" (*id.*) and that the references would have provided one of ordinary skill with a reasonable expectation of success (*id.*).

Appellants argue that the claimed methods require a first step of generating virtual compounds, followed by steps of synthesizing and testing the actual compounds (Br. 18). Appellants argue that "[i]n contrast, the methods reported in the Agrafiotis reference *begin* with the *actual* synthesis of members of the physical library . . . prior to testing the totality of the

physical library members for a desired property" (*id.*). Only after synthesizing and testing the library of actual compounds, Appellants argue, does Agrafiotis "select a subset of the physical members of the physical library to generate their virtual lib[r]ary and subsequent synthesis instructions" (*id.*). Appellants state that they "are unable to locate any portion of the Agr[a]fiotis reference that teaches generation or evaluation of *in silico* or virtual compounds according to defined criteria *prior* to their synthesis or assay" (*id.* at 19).

The Examiner responds that Appellants "have, by their own arguments, admitted that AGRAFIOTIS teaches BOTH in generation of a virtual (or in silico) library and synthesis of compounds" (Answer 8). The Examiner argues that because Agrafiotis' process is reiterative, Agrafiotis discloses a step of generating virtual compounds before the actual compounds are synthesized and tested (*id.*). The Examiner also points out that "the instant claims recite open claim language, and thus do not exclude additional steps such as those also taught by AGRAFIOTIS" (*id.*).

We agree with the Examiner that Agrafiotis discloses a process comprising a step of generating virtual compounds, followed by the steps of synthesizing and testing the actual compounds. Agrafiotis discloses that the process is to be repeated (Agrafiotis, Figure 2). After the steps of robotic synthesis (Agrafiotis, Figure 2, item 112) and analysis (*id.* at Figure 2, item 116), the information obtained is used to create a structure-activity database (*id.* at Figure 2, item 122). Thus, Agrafiotis discloses generating a set of virtual compounds, as recited in claim 55.

When Agrafiotis' process is repeated, the information in the structure-activity database is used to guide the subsequent robotic synthesis and testing of the actual compounds (*id.* at Figure 2). Thus, when Agrafiotis' process is repeated, the step of generating the virtual compounds precedes the steps of synthesizing and testing the actual compounds, as recited in claim 55.

We note that Agrafiotis' process has steps that precede generating the virtual compounds, and that these steps include synthesizing actual compounds. However, as pointed out by the Examiner, the claims use the transitional term "comprising" to define the process, and therefore do not exclude Agrafiotis' additional steps. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps. Claim 1 uses the open-ended transition 'comprising' to introduce the recited steps. Thus the claim signals to patent practitioners that claim 1 allows activity . . . before the recited steps." (citations omitted)).

Appellants argue that, at column 11, lines 57-65, Agrafiotis discloses that the analysis robots can incorporate additional physical and/or electronic property analysis modules to provide physical and/or electronic property data regarding the analyzed compounds (Br. 19). Thus, Appellants argue, "this portion of the Agrafiotis reference relied upon in the Office Action supports the notion of obtaining physical and/or electronic property data related to the actual compounds already synthesized, and not to using thermodynamic criteria with other criteria to generate *in silico* compounds"

(*id.*). Appellants similarly argue that at columns 16 to 17, Agrafiotis discloses the synthesis of a library of actual compounds, and that "[n]owhere does this portion of the Agrafiotis reference teach using thermodynamic criteria with other criteria to generate *in silico* compounds" (*id.* at 20).

We are not persuaded by this argument. As discussed above, Agrafiotis discloses a process having the same basic steps in the same order as recited in the claims. The open language in Appellants' claims encompasses any additional steps Agrafiotis might disclose.

To the extent that Agrafiotis does not explicitly disclose using thermodynamic properties as a selection factor, the Examiner has applied Uhlmann to demonstrate that hybridizing and melting temperatures were important considerations when preparing therapeutic antisense oligonucleotides. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). Thus, the fact that Agrafiotis does not suggest all of the claims' limitations does not demonstrate nonobviousness, because Uhlmann establishes that one of ordinary skill using Agrafiotis' methods to prepare antisense oligonucleotides would have applied thermodynamic criteria to the analysis.

Appellants argue that the fact that "the databases reported in the Agrafiotis reference may be in a computer readable format does not mean that the compounds produced by using thermodynamic criteria with other

criteria are also *in silico* compounds. Indeed, it appears that these two databases are used for the actual generation of real compounds" (Br. 19).

We are not persuaded by this argument. By its name, it is clear that the structure-activity database contains information regarding the structure and biological activity of chemical compounds. Because the compounds in the database are in the form of information, rather than actual synthesized compounds, the compounds in the database meet the limitation requiring *in silico* compounds.

To summarize, Appellants' arguments do not persuade us that the Examiner erred by concluding that claim 55 would have been obvious over the cited references. We therefore affirm the Examiner's obviousness rejection of claim 55. Because they were not argued separately, the remaining claims fall with claim 55.

SUMMARY

We reverse the Examiner's new matter rejection and affirm the Examiner's obviousness rejection.

AFFIRMED

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